An integrative approach for model driven computation of treatments in reproductive medicine

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An Integrative Approach for Model Driven Computation of Treatments in Reproductive Medicine

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January 18, 2016

Abstract

We present an overview of the current status of the European collaborative project PAEON. The challenge of PAEON is to provide specialists in reproductive medicine with a computerised model of the menstrual cycle under normal and various pathological conditions, which will allow them to get further insight in fertility dynamics. This model also enables the simulation of treatment protocols, which were used within in vitro fertilization. By the definition of virtual patients through biologically admissible parametrizations our approach allows not only the evaluation of a given treatment strategy *in silico*, but also the design and optimization of such protocols. Once a protocol is formalized in the virtual hospital, the success can be controlled by a treatment execution monitor, which works then as a clinical decision support system. All these tools will be combined in a virtual hospital environment, enabling the access to the PAEON services through the web.

Contents

1 Introduction

For many couples, having children is one of the major life aims. Failure is associated with guilt, inadequacy and loss of the sense of life, bearing an increased risk for negative psycho-social functioning, such as depression and anxiety disorders [8, 9, 11]. Furthermore, changes in population demographics, greater focus on education and careers among women have resulted in great numbers of women attempting pregnancy at older ages when they are inherently less biologically fertile. In Europe, for example, infertility affects 10% to 15% of couples of reproductive age, and experts assume that these figures will double in a decade [5, 13].

Investigation and treatment of infertility is directly and indirectly (by time consuming medical consultations, expensive medical techniques, limited success rates leading to repetitive treatment attempts, time-off from work, etc.) associated with high expenses for the individual as well as for the society. Indeed, costs for individual couples in Europe are around 10% of annual household expenditures [3]. Overall, infertility in Europe costs approximately 1 billion Euros per year.

In about 50% of the cases, infertility is caused by female health problems, more than 40% of which are related to endocrinologcal diseases. Human fertility is based on physiological events like adequate follicle maturation, ovulation, ovum fertilisation, corpus luteum formation as well as endometrial implantation, proceeding in a chronological order. Diseases such as endometriosis, Prolactin (PRL) associated disorders or Polycystic Ovary Syndrome (PCOS) seriously disturb menstrual cycle patterns, oocyte maturation and consequently fertility; pelvic endometriosis, occurring in up to 40% of infertile women, is a hormone dependent disease characterised by ectopic proliferation of endometrial cells, which occurs nearly exclusively during the reproductive phase. Beside endocrine diseases, several environmental and lifestyle factors have a negative impact on fertility: up to 13% of female infertility may relate to smoking. Obesity, which increases not only in European countries, is associated with menstrual dysfunction, decreased fertility, as well as increased risks of miscarriage.

Modern Assisted Reproductive Techniques (ART), like In Vitro Fertilisation (IVF) or Intracytoplasmatic Sperm Injection (ICSI), have nowadays dramatically increased the chances for successful reproduction. Nevertheless, current success rates reach only 35% even in leading clinical centers. Many of the pathophysiological effects of endocrine diseases and environmental/lifestyle factors on fertility as well as dynamics in fertility treatment still remain unclear. Thus, a better understanding of the endocrinological concert orchestrating the physiology of fertility would open new opportunities for therapeutic options for improved natural fertility as well as success rates in ART.

We address this problem by using a systems biology approach that aims at integrating clinical data collection with mathematical modeling of the complex biological system. Although the relevant components and feedback mechanisms have been identified from experiments and have been described qualitatively for many years, dynamic (time-dependent) mathematical models that permit medically sound *quantitative predictions* for the periodic changes in hormone levels and follicular function have started to be developed only a few years ago. In fact, even though half of the world's population is female, the menstrual cycle has so far received comparably little attention in systems biology.

For these reasons, since 2013 the European Commission has been funded the collaborative research project PAEON-"Model Driven Computation of Treatments for Infertility Related Endocrinological Diseases" within the EU VPH (Virtual Physiological Human) initative. The project consortium consists of the Sapienza University of Rome, the Lucerne University of Applied Sciences and Art, the Hannover Medical School, the University Hospital Zurich, and the Zuse Institute Berlin.

The PAEON project rests on three main components, whose objectives may be summarised as follows.

1. *Define a mathematical model of the human menstrual cycle which is able to simulate the healthy cycle as well as infertility-related endocrine disorders. This model should also enable individualized, patient specific models.*
   Existing models of the human menstrual cycle were usually constructed for very specific purposes, e.g. GynCycle [10] for simulating GnRH analogue treatment, models for analysing prolactin patterns [4] or the follicular development [2]. None of these models is able to simulate whole cycles in which pathological hormone concentrations go along with insufficient follicular development. Our goal is to enrich and combine these models with components and mechanisms involved in endocrine disorders like PCOS or endometriosis, also taking into account external factors (e.g. drugs) as well as environmental factors. Furthermore, the models should allow also the realistic simulation of individualised treatment strategies (protocols).

2. *Develop a Virtual Hospital (VH) combining mathematical models of the treatment and the individual patient.*
   The availability of a mathematical model of both the individual patient and the medical treatment allows an innovative perspective based on a system control engineering approach, if one regards the system composed of the treatment and the patient as a feedback-loop control system, where the physician acts as a feedback-loop controller for the patient. This view enables us to use powerful control engineering and computer science methods for its analysis. A medical treatment protocol generally asks to take certain measurements on the patient and, depending on their outcome, suggests certain actions. Actions consist of, e.g., taking further measurements or administering specific amounts of certain drugs. We regard a medical treatment as a computer procedure that, observing patient measurements, strives to steer them towards optimal values for the number and size of mature follicles at the end of the treatment.

3. *Perform measurements or collect data from available databases to permit validation and refinement of currently available models.*
   The presently available models are based on small study samples and include only a part of the parameters relevant for the regulation of the human menstrual cycle. Therefore they need validation with larger samples not only from normally cycling women but also hormonal secretion patterns from patients suffering from endocrinological diseases such as endrometriosis, PRL-associated disorders, or PCOS. Even though this is a tedious and expensive part of our project we will focus here only on the first two main parts of PAEON.

2 Models of the hormonal cycle and treatment protocols

2.1 Models of the healthy female hormonal cycle

In order to construct a physiological model, species or components (e.g. hormones, follicular properties) and mechanisms (inhibition, stimulation, chemical reactions) that are essential for the regulation of the menstrual cycle have to be determined. Within the hormonal cycle, the most important compartments are the hypothalamus, the pituitary gland, and the ovaries, connected by the bloodstream. They are generally referred to as the Hypothalamic-Pituitary-Ovarian (HPO) axis. During the reproductive cycle, hormones of the HPO-axis fluctuate periodically, leading to the formation of cycles with a period of typically 28 days, see Figure 1.

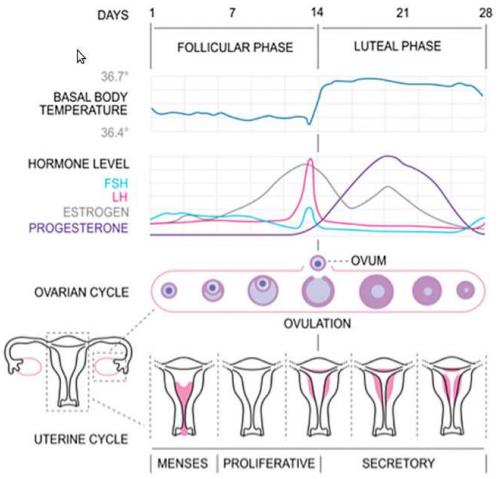
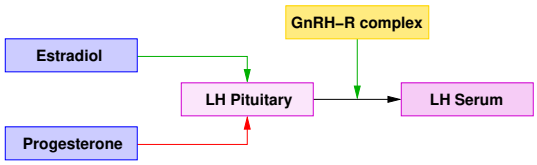


Figure 1: Schematic sketch of the female hormonal cycle

A model of the hormonal cycle has to deliver a qualitative description of the following regulatory circuits. In the hypothalamus, the hormone GnRH (gonadotropin-releasing hormone) is formed, which reaches the pituitary gland through a portal system in pulses and stimulates the release of the gonadotropins luteinising hormone (LH) and follicle stimulation hormone (FSH) into the bloodstream. The gonadotropins regulate the multi-stage maturation process of follicles in the ovaries (follicular phase). The number of follicles that mature is dependent on the amount of FSH available to the gonad and the sensitivity of the follicles to the gonadotropins. During that phase, the maturing follicles secrete mainly estradiol (E2) and inhibin B. If gonadotropin stimulation is adequate, one of the several follicle units will advance to ovulation. Any disequilibrium in the amount and timing of involved hormones may result in reduced oocyte quality unsuitable for fertilisation. During the following luteal phase the corpus luteum secrets mainly progesterone but also E2 and inhibin A. Through the blood, these hormones reach the hypothalamus and pituitary gland, where they again influence the formation of GnRH, LH, and FSH. The cycle starts anew

with the menstrual bleeding initiated by the decreased progesterone secretion from the corpus luteum.

Once the medical and biological mechanisms have been formulated in a qualitative manner, the next step is to translate them into quantitative mathematical equations. Since we are mainly interested in the answer of a given system (the human menstrual cycle) to disturbances (e.g. treatments), this can only be modelled by time-dependent equations, e.g. ordinary differential equations (ODEs) or differential-algebraic equations. To formulate the differential equations of a quantitative mathematical model, the physiological and biological processes that occur must be known very accurately. However, the exact chemical reaction mechanisms are often not understood in sufficient detail; often one only knows whether certain hormones have a stimulating or inhibiting effect on other hormones. In semi-quantitative modelling of such switch behaviour, Hill functions are used. If the reaction mechanisms are known more specifically, for example from data bases, more detailed equations can be formulated. Figure 2 illustrates this approach for the LH submodel and the corresponding ODEs. If all processes are included, one obtains a usually "large" system of differential equations. The qualitative dependencies of our model are visualised in Figure 3.



$$\mathrm{Syn_{LH}}(t) = (b_{\mathrm{Syn_{LH}}} + m_{\mathrm{E2}} \cdot H^{+}(\mathrm{E2}, T_{\mathrm{E2}}, n_{\mathrm{E2}})) \cdot H^{-}(\mathrm{P4}, T_{\mathrm{P4}}, n_{\mathrm{P4}})$$
$$\mathrm{Rel_{LH}}(t) = (b_{\mathrm{Rel_{LH}}} + m_{\mathrm{GnRH\text{-}R}} \cdot H^{+}(\mathrm{GnRH\text{-}R}, T_{\mathrm{GnRH\text{-}R}}, n_{\mathrm{GnRH\text{-}R}})) \cdot \mathrm{LH_{Pit}}(t)$$
$$\frac{d}{dt}\mathrm{LH_{Pit}}(t) = \mathrm{Syn_{LH}}(t) - \mathrm{Rel_{LH}}(t)$$
$$\frac{d}{dt}\mathrm{LH_{blood}}(t) = \frac{1}{V_{\mathrm{blood}}}\mathrm{Rel_{LH}}(t) - k_{\mathrm{on}} \cdot \mathrm{LH_{blood}} \cdot R_{\mathrm{LH}} - c \cdot \mathrm{LH_{blood}}$$

Figure 2: LH model and the corresponding ODEs. H^{+} and H^{-} are stimulating and inhibitory Hill functions with thresholds T and exponents n. LH production in the pituitary is stimulated by E2 and inhibited by Progesterone (P4). The release of LH into the blood is stimulated by the GnRH-receptor complex, if its concentration is higher than some threshold.

Hence, an initial value problem (IVP) can be formulated, where the change in the species y depends both on the species themselves and on a parameter vector p. Such autonomous (i.e. not explicitly time dependent) equations are usually used to describe closed systems, whereas non-autonomous (i.e. explicitly time dependent) equations will be used, for example, to model environmental factors or drug administrations that change with time. Moreover, it is assumed that some discrete experimental data (in form of species concentrations versus time) are available. Usually, only a certain amount of the species concentrations are measurable observables. The task at hand now is to quantify the unknown parameters and initial values by comparing model values with the measured data. A complete data set, of course, must also include statistical tolerances

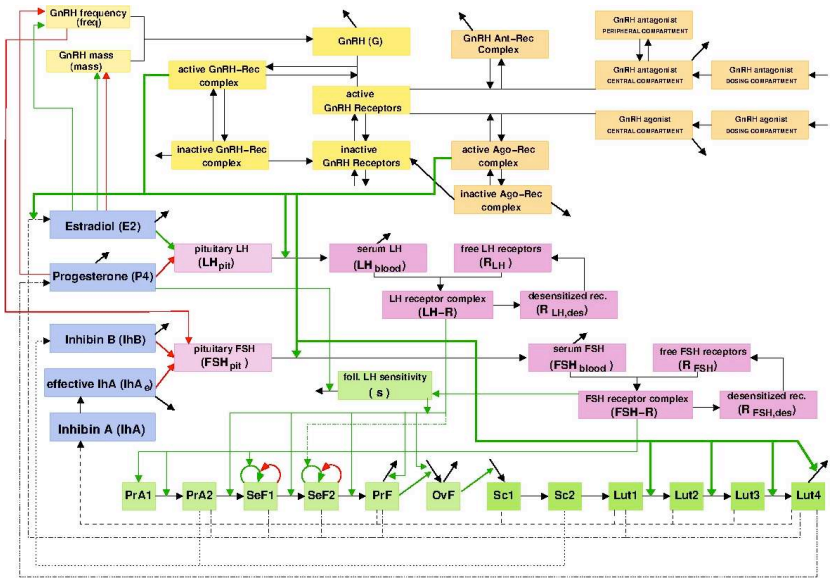


Figure 3: Flowchart of the GynCycle model for the human menstrual cycle with 33(+8) ODEs, 114 parameters

for each measurement. This task may be computationally solved by appropriate Newton algorithms (local search) or stochastic approaches (global search). As an example, Figure 4 depicts the results of parameter fitting to a set of experimental data from 12 normally cycling women for LH, FSH, P4, and E2.

2.2 Treatment modelling

Even if there exists a number of newer approaches (e.g. the antagonist protocol), there are two methodologies which, depending on the age and other conditions, are the most commonly used treatments. They consist of two phases, he suppression of FSH and LH by GnRH (downregulation, long protocol) or by P4 (preparation, short protocol), followed by a usually two weeks long stimulation phase with the combined administration of GnRH agonists, FSH, and LH. Within the second phase one tries to stimulate follicle growth in order to induce growth of a cohort between 5 and 15 follicles aiming to have as many ripe oocytes in one cycle as possible. The actual follicle maturation is monitored by transvaginal ultrasound and E2 blood levels. Future follicle growth can be estimated from biological age, anti-Müllerian hormone (AMH) levels, FSH and the antral follicle count (AFC). Hormone doses for the stimulation treatment are based on this estimation. Too modest dosages of hormones are associated with the risk of an insufficient number of oocytes, too aggressive treatments, especially in patients with PCOS, are associated with a high risk of overstimulation syndrome and a reduced quality of obtained oocytes. If the result with respect to AFC and E2 levels are satisfactory, ovulation will be induced by one additional higher dose of LH.

In many cases, the drugs administered differ considerably from their nat-

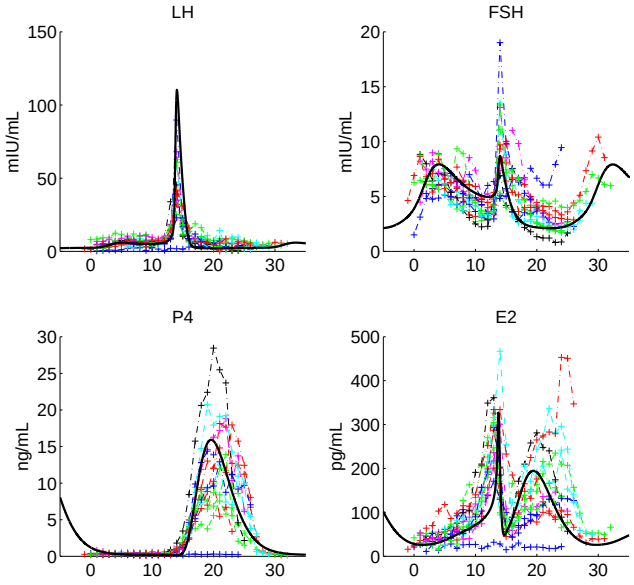


Figure 4: Results of parameter estimation for the GynCycle model to 12 normally cyling women

ural counterpart in their chemical structure, metabolism, and activity. It is therefore more reasonable to construct a separate differential equation for the concentration $c(t)$ of each administered substance,

$$\frac{dc\,(t)}{dt} = \Phi\,(t) - c_L c\,(t)\,, \tag{1}$$

with a time dependent source term $\Phi(t)$ and a clearance term c_L. The solution of this equation may then be used in other equations where the drug and/or its natural counterpart has an effect.

In most cases, drug administration leads to plasma concentration profiles with a left-skewed peak. These time courses are usually described by some pharmacokinetic parameters. A commonly accepted approach is, e.g., to measure the peak plasma concentration $c_{\max}$, the time point $t_{\max}$ of this maximum, and the integral over the concentration-time curve, $AUC_{0-\infty}$ (area under the curve).

Within our model of the hormonal cycle we have successfully modelled such profiles based on the probability density function of the gamma distribution with fixed parameter $\alpha = 2$. This approach leads to the following differential equation for the drug concentration,

$$\frac{dc\,(t)}{dt} = D\beta^2 t \exp\left(-\beta t\right) - c_L c\,(t)\ , \tag{2}$$

where the parameter D represents the amount of the drug administered. The parameters β and c_L can easily be determined numerically on the basis of mea-

sured values $c_{\max}$, $t_{\max}$, and $AUC_{0-\infty}$. A similar approach is also possible in terms of other pharmacokinetic parameterizations, e.g. the volume of distribution, the clearance rate or half-life times[1]. With this methodology, we are able to use all different pharmacological data available in the literature [1], and to store them in a common data base for all drugs relevant in clinical practice. Figure 5 presents preliminary results for a simulation of the long protocol. In addition, our model enables not only the simulation of normal healthy cycles with and without treatments, but also the simulation of other limit cycles as they are typical for, e.g., PCOS.

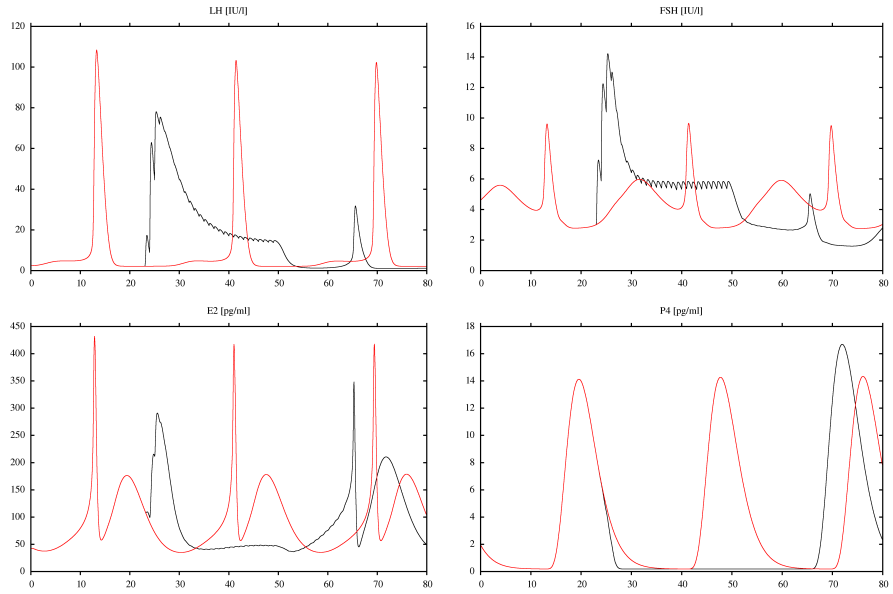


Figure 5: Results of a simulation of a whole long protocol for LH, FSH, E2, and P4 (black) compared with the normal hormonal cycle (red). The downregulation with the GnRH agonist Triptoreline lasts 27 days (cycle days 23 until 50), the stimulation then lasts 14 days. The rise of E2 during stimulation indicates a successful treatment.

2.3 Patient-specific models

Unfortunately, a fully automatic procedure that just computes values for the model parameters that fit the (few) available measurements (*parameter identification*) typically leads to species behaviours that, while being mathematically correct solutions to the ODE model, are meaningless from a biological point of view. Moreover, we have to take into account that the parameter value space is huge.

We overcome the above mentioned obstacles by splitting our computation into two phases: an *off-line* phase that narrows our search space, and an *on-line*

[1]Since GnRH is active only in the brain, the GnRH agonists blood levels are not responsible for the effects of the administration. We have, therefore, implemented a simple compartment model for GnRH.

phase that computes patient-specific predictions. The first phase produces an almost *complete* set of biologically sound parameter values, whereas the second phase selects the parameter value that minimises the mismatch between model predictions and patient measurements.

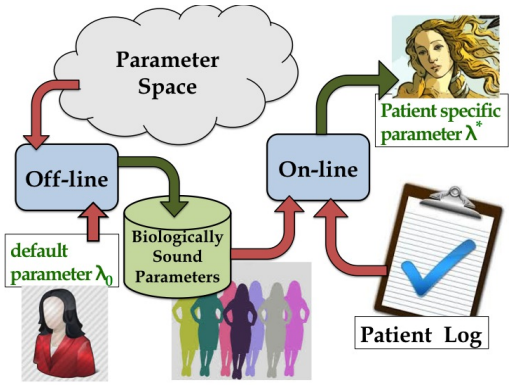


Figure 6: Architecture of the patient-specific parameter identification procedure

The overall architecture of our approach is depicted in Figure 6. Starting from a default parameter value λ_0 that results from our accepted standard model, the off-line procedure extracts from the parameter value space a complete set S of biologically sound parameter values. *Biological soundness* asks for S to contain *only* parameter values leading to biologically meaningful time evolutions for the species in the model. *Completeness* asks for S to include *all* parameter values leading to biologically meaningful behavior for the model. The on-line phase selects the parameter value in S that best fits with patient measurements, searching in the set of biologically sound parameters computed in the off-line phase.

Intuitively, we search for parameter values λ that lead to trajectories $x(\lambda, t, u)$, with u an external time-dependent input function, e.g. a treatment, that are both quantitatively and qualitatively similar to the trajectory $x(\lambda_0, t, u)$. We capture the fact that two trajectories are similar (i.e. they differ because of a "shift" and/or a "stretch") by introducing three measures of similarity. The *cross-correlation* $\rho_{\lambda_0,\lambda,i}$ measures qualitative aspects of the trajectories $x_i(\lambda_0, t, u)$ and $x_i(\lambda, t, u)$ (for example, if they have the same peaks) whereas the *average normalised differences* $\mu_{\lambda_0,\lambda,i}$ and the *normalised differences of autocorrelations* $\chi_{\lambda_0,\lambda,i}$ are two measures of the average distance between $x_i(\lambda_0, t, u)$ and $x_i(\lambda, t, u)$. Biological soundness of the parameter λ with respect to λ_0 requires that differences between $x_i(\lambda_0, t, u)$ and $x_i(\lambda, t, u)$ in terms of these three measures are below given thresholds. Our goal is to identify a set of biologically sound model parameter values that describes as many biologically meaningful behaviours as possible but, at the same time, is not too large in order to speed up our on-line computation. The first phase of our procedure finds (with high confidence) the set S of all *biologically sound* parameter values with respect to a default parameter λ_0. The set S is computed by checking parameter values in a finite subset $\hat{\Lambda}$ of Λ (*discretised parameter space*).

Since the number of parameters to be identified is quite large (75 in our case

study) the discretised parameter space is huge (10^{75} if we consider 10 possible values for each parameter), thus making an exhaustive search in the discretised parameter space $\hat{\Lambda}$ unfeasible. To overcome such an obstruction, we followed an approach inspired by statistical model checking [6, 7]. At the end, the set S contains *only* and (with arbitrarily high confidence) *all* biologically sound values for the patient-specific parameters. Note that such an algorithm does not depend on patient-specific data. Thus it must be run *off-line* once and for all, and its output (the set S) can be stored for further processing. The computation of an appropriately large set of biologically admissible (BA) parameters may need several days even on a cluster with many CPUs. Details of the approach can be found elsewhere [12]. The biologically admissible parametrizations may be interpreted also as *virtual patients*.

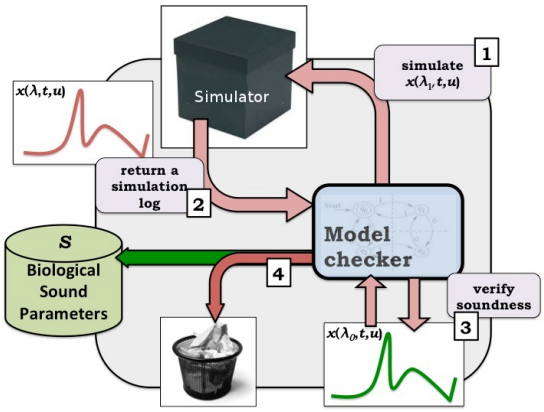


Figure 7: Architecture of *off-line* computation of biologically sound parameters

The architecture of our algorithm is shown in Figure 7. A model checker randomly generates parameter values λ in the discretised parameter space $\hat{\Lambda}$ (point 1 in the picture). The simulator is called for a simulation of $x(\lambda, t, u)$ and returns a file containing a set of points of the trajectory $x(\lambda, t, u)$ (point 2). At this point, this trajectory is compared with the trajectory $x(\lambda_0, t, u)$ obtained by considering the default parameter λ_0 (point 3). If $x(\lambda, t, u)$ passes the biological soundness test, λ is added to the set S of biologically sound parameters, otherwise it is discarded (point 4).

The algorithm stops when N attemps fail to find a biologically sound parameter. Given two positive real numbers δ and ε, N is chosen in such a way that with confidence $1-\delta$ the probability of finding other biologically sound parameter values not in S is less than ε. The results in Figure 8 demonstrate the variability of the individual time courses. In this computation, the algorithm has found more than 7000 different BA parametrizations.

3 PAEON Virtual Hospital (VH)

One of the main goals of the PAEON project is to provide effective computational tools as Web-based services through a Web portal named Virtual Hospital (VH), in order to aid medical researchers and doctors in their everyday work.

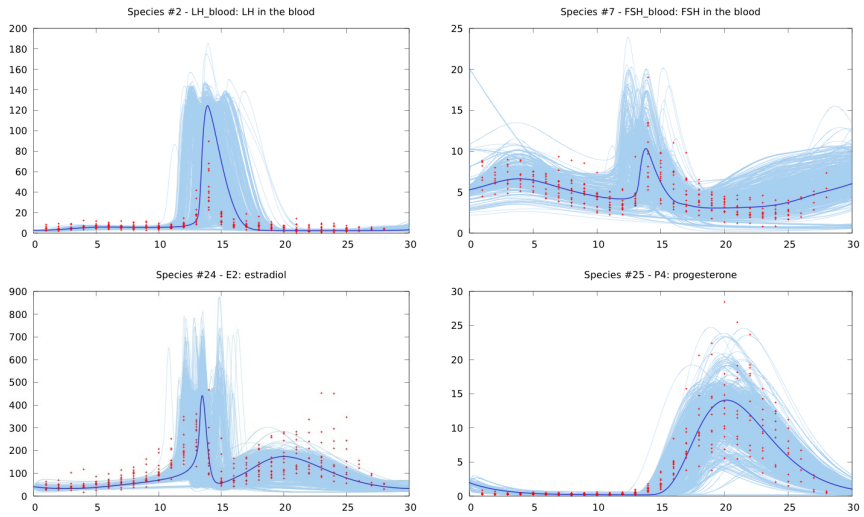


Figure 8: Results of the *off-line* computation of all biologically parametrizations for LH, FSH, E2, and P4 compared with 12 normal hormonal cycles.

The PAEON VH Web-application will enable researchers, within and outside the PAEON project, to exploit results by providing services to: 1) upload/download models and results from clinical trials or from computations, 2) use the computational tools developed in the project. Furthermore, VH will support the iterative refinement approach of our project by acting as a coordination tool between the modelling activities, the computational tool development and the clinical trials.

VH will provide access and data security services compliant with clinical data and security policies along with a graphical user interface to seamlessly fit into hospital environments and thus clinicians needs. This in turn will allow the hospitals in our consortium to insert (anonymised) experimental data that, via the VH, are immediately available to the research partners working on modelling or model analysis tools. This guarantees constant alignment between the modelling/computation activities and the clinical trial activities. The VH Data Repository will provide a knowledge base for storing (generic) models, patient-specific models (digital patients), treatment protocol models (digital physicians), anonymised experimental results from the clinical trials, and experimental results from running PAEON computational tools on given clinical data. The overall PAEON VH software architecture is sketched in Figure 9.

Here, we will describe only some of the computational services, namely the Treatment Execution Monitor (TEM), the Model-Based Verification of Treatment Protocols (MBV-TP), and the Model-Based Design of Individualised Treatment Protocols (MBD-ITP).

3.1 Treatment Execution Monitor

Within TEM, protocol models keep track of the status of a *treatment protocol* for each patient under treatment, and suggest *actions* to clinicians. In a treatment

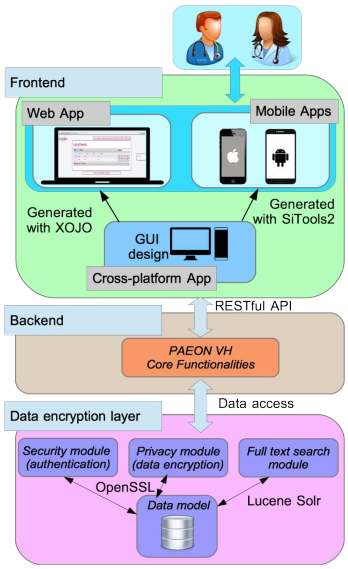


Figure 9: PAEON VH Software Architecture

protocol, typical actions are: when to administer a drug, the dose, and when to take next measurements. A clinical treatment protocol is a description of a complex activity that involves decisions during the treatment execution. In Figure 10 the overall structure of a treatment protocol is sketched.

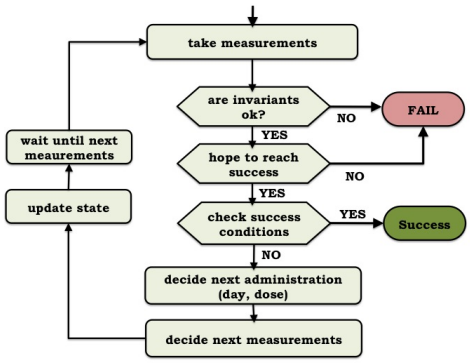


Figure 10: General structure of a treatment protocol

The TEM is a tool designed to support clinicians during treatment protocols. It behaves as a Clinical Decision Support System (CDSS) that, on the basis of the modelled treatment protocol and the recorded treatment data (patient data, patient measurements), suggests actions (e.g., timing and amount of drug to be administered) to clinicians. TEM takes as input a formalised treatment model and provides as output what the protocol prescribes in a given situation.

4.5. **Mid-time measurement step**:

4.5.1. On day "End preparation day" + 3 or day "End preparation day" + 4 (no medical reason, just logistic reasons), measure E2 and P4 (lab requires 3 hours to provide values):

4.5.1.1. if $E2 \geq 250$ pmol/l and $P \geq 6$ nmol/l, then Halt the protocol.

4.5.2. Wait till the end of the day defined in Req. 4.5.1.

4.6. **Stimulation phase**:

4.6.1. We call the current day "Day 1 (of the stimulation phase)". "Day 1" is "End preparation day" + 4 or "End preparation day" + 5 (depending on the choice taken in Req. 4.5.1.). This day is always a Friday, given Req. 4.4.5.

4.6.2. The last day of the stimulation phase is the day when we induce ovulation. This day will be called "ovulation induction day" in the following. It will be a day between Day 8 and Day 13 (of the simulation phase).

4.6.3. From "day 1 of the stimulation phase" until the "ovulation induction day", administer D 0.1mg/day

4.6.4. From "stimulation drug administration start day" (as chosen as in Req. 4.3.) until the "ovulation induction day" (as defined as Req. 4.6.2.), administer the chosen stimulation drugs (as decided in Req. 4.2.3.) each day

4.6.5. On day 6 (of the stimulation phase), measure E2 and P4:

4.6.5.1. If $E2 < 500$, then change the doses for days 6 and 7 of the drug(s) (as chosen in Req. 4.2.3. and Req. 4.2.5.) into:

Figure 11: Part of a treatment protocol currently in use at UZH

```
Trans
       s'= if (dayStim==0 & (e2Input > 250 | p4Input > 6)) then FAIL
          else if (dayStim == 5 & p4Input >= 40) then FAIL
          else if (dayStim > 8 & follicleCount(fpCurrent)<3) then FAIL
          else if (day == 0) then DOWNREGULATION
          else if (day == downLength) then STIMULATION
          else s;
       day'= day+1;
       dayStim'= if (day >= downLength) then (dayStim + 1) else dayStim;
       e2'= if (dayStim == 0 | dayStim == 5 | dayStim == 8)
          then e2Input else e2;
       p4'= if (needP4 & (dayStim == 0 | dayStim == 5 | dayStim == 8))
          then p4Input else p4;
       needP4'= if (dayStim == 5 & p4Input < 4) then false;
       doseStim'= if (dayStim == 0)
              then computeDoseStim(age,amh,afc)
              else if (dayStim == 5)
                 then changeDoseStim(age,amh,afc,e2Input,doseStim)
                 else doseStim;
       fpLast'= if (dayStim == 8 | dayStim == 11 | dayStim == 13)
          then fpCurrent
          else fpLast;
       fpCurrent'= if (dayStim == 8 | dayStim == 11 | dayStim == 13)
              then FollicleProfile
                 .fs9 = fs9Input, .fs10_11 = fs10_11Input,
                 .fs12_13 = fs12_13Input, .fs14_15 = fs14_15Input,
                 .fs16_17 = fs16_17Input, .fs18_19 = fs18_19Input,
                 .fs20 = fs20Input
              else fpCurrent;
```

Figure 12: Part of the protocol strategy used at UZH in formalized description

Physicians can follow the suggestions of TEM or override them. In any case, all decisions are recorded by TEM and possibly used during future treatments.

In order to model fertility treatments currently in use, we have designed and implemented the Vanilla Automata Language (VAL) language. After a careful analysis, carried out by computer scientists together with clinicians, the protocols currently in use at the University Hospital Zurich (UZH) were implemented in VAL. Instead of explaining the details of VAL, Figures 11 and 12 show a small section of the protocol as used at the UZH and the formalized counterpart.

The TEM GUI we have designed can already be used for training or educational purposes in reproductive medicine departments. Furthermore, other clinics could compare their own protocols with those of the UZH, one of the leading clinics in reproductive medicine in Europe. We are planning also to include the administration strategies of other European reproductive medicine centers with high success rates into TEM.

3.2 Model-Based Verification of Treatment Protocols (MBV-TP)

The MBV-TP computational service aims at evaluating, *in silico*, the effectiveness of a treatment protocol by executing treatment simulations. Simulations will be performed on a model that consists of a VPH model and a treatment model for (subsets of) all biologically admissible (BA) parameters.

Since treatment protocols are designed to work on all patients (or at least a class of patients), they adapt dosages and duration of drug administration to patient measurements. In this scenario, it is reasonable to address the problem of verifying that a given treatment protocol reaches its goal *for each* possible patient, or, more realistically, evaluating its success rate. In our model based approach this means that, since treatment models adapt their behaviour to the biological model behaviour, treatment protocol verification consists of checking if the treatment reaches its goals *for a large number* of BA parameter values.

Treatment goals have been generalised using the notion of *Key Performance Indicators* (KPIs). A KPI provides a measure of the effectiveness of a treatment. This allows to evaluate treatments from different points of view, each of which is formalised as a KPI. In the context of fertility treatments considered in the PAEON project, the treatment model is an executable description of a fertility treatment currently in use in clinical practice. The biological model is a model of the menstrual cycle together with a pharmacokinetic model for drug administration, and the KPIs are related to, e.g. E2 levels, number and size of follicles, and the total amount of administered drugs.

MBV-TP takes the following inputs:

- a parametrised treatment protocol
- values for all treatment parameters, so that one obtains a specific treatment
- the set of BA parameters on which the treatment will be verified
- a set of KPIs associated to the treatment

and yields the following output:

- values for all the KPIs given as input, for each given BA VPH model parameter.

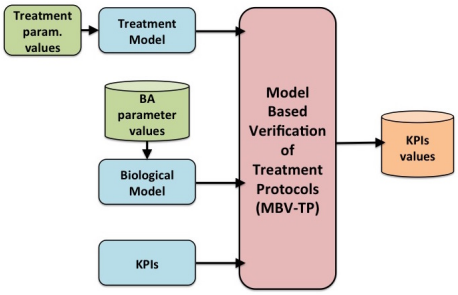


Figure 13: MBV-TP inputs and outputs

In Figure 13 the overall structure of MBV-TP is sektched. As an example, we can evaluate if the treatment under consideration ensures *safety conditions* (in our context they are evaluated mainly by checking E2 levels, to check the risk of overstimulation), and the percentage of BA parameter values for which the treatment is successful.

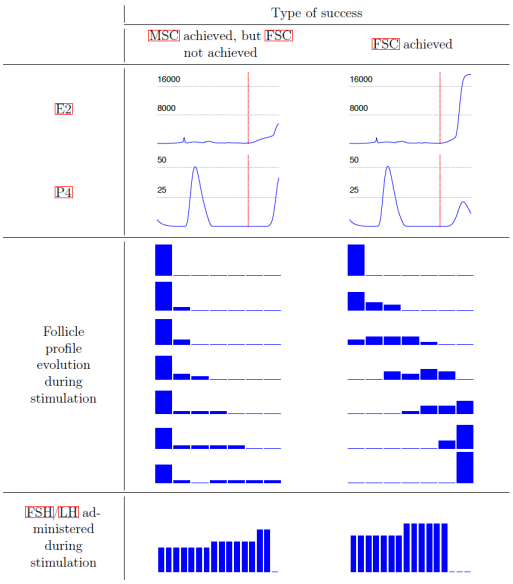


Figure 14: VPH model evolutions computed by MBV-TP, showing treatment successes

In Figure 14. the right column shows the VPH model evolution under a sample BA model parameter (virtual patient) for which the treatment succeeds, achieving a full success condition (FSC). It can be observed that the E2 and P4 levels are always below their safety thresholds, and that the follicles gradually

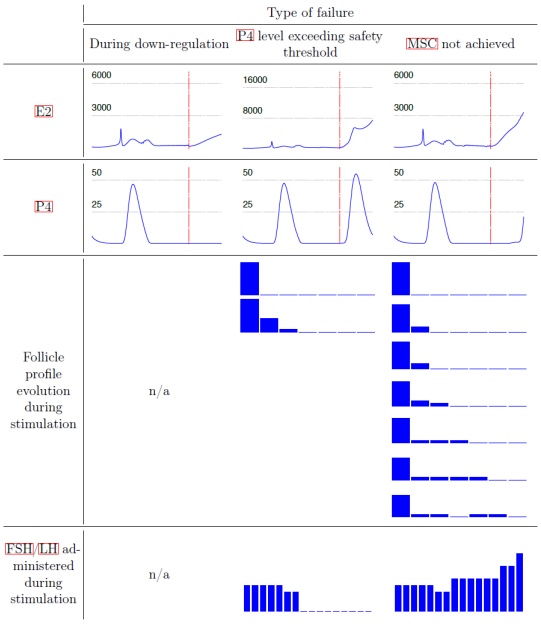


Figure 15: VPH model evolutions computed by MBV-TP, showing treatment failures

grow during stimulation (letting the treatment achieve FSC). The left column of Figure 14 shows another treatment success case, but in this case only a minimum success condition (MSC) is achieved (and, in fact, only three follicles reach maturation stage).

To see an example where the treatment fails, consider the right column in Figure 15, showing the VPH model evolution under a sample BA model parameter (virtual patient) for which the treatment does not achieve MSC. It can be seen that follicles do not grow satisfactorily, and that the treatment correctly reacts to such a slow follicle growth by increasing the daily dose of the stimulation drug (from 300 IU to 450 IU), as safety thresholds for E2 and P4 are far from being reached. Notwithstanding treatment adaptations, only two follicles reach maturation. The first two columns show two interrupted treatments due to unsuccessful down-regulation (left) and P4 safety threshold reached during stimulation (centre). In the first case, the follicle profile is not shown at all (as stimulation is not started), while in the second, stimulation is interrupted due to an too early P4 peak.

3.3 Model-Based Design of Individualised Treatment Protocols (MBD-ITP)

MBD-ITP aims at supporting medical doctors and researchers in the design of individualised treatments in a clinical setting, by automatically evaluating the effectiveness of a treatment protocol over a set of possible values for the treatment parameters. Compared to the verification task, the individualised treatment design activity deals with more complex treatments. The main ingredient

of our treatment synthesis approach is the definition of *parametrised treatment* models. Instead of synthesising a treatment from scratch, we take a template treatment with parameters and find suitable values for these parameters.

Parametrised treatments have essentially the same structure of treatments currently in use in clinical practice, but their execution depends on some parameters. Having the same structure of the template treatment, they are more likely to be accepted in the clinical practice. Example of treatment parameters are thresholds that influence treatment decisions, or doses of administered drugs. Moreover, as in the treatment verification task (MBV-TP), we consider a set of KPIs to evaluate treatment effectiveness.

Therefore, our approach to the treatment synthesis problem consists of solving a search problem over the set of possible treatment parameter values, looking for the treatment parameter values that optimise the KPIs. Since the optimisation of a set of KPIs is a multi-objective optimisation problem, we select all those treatment parameter values that lead to a tuple of KPIs values that are not *Pareto dominated* by other treatment parameter values.

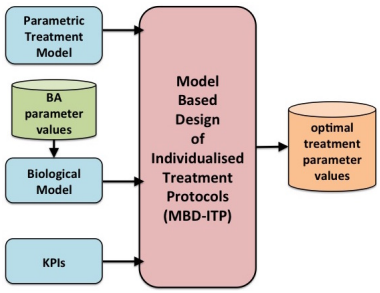


Figure 16: MBD-ITP inputs and outputs

The input for MBD-ITP ist the same for MBV-TP except that it needs additionally a parameterized treatment. The output is correspondingly a set of parameter vectors, each treatment parameter vector defines an individualised treatment which is considered optimal with respect to the set of given KPIs and for the set of BA VPH models, see Figure 16.

This approach is computationally demanding. We ran MDB-ITP on 15 Xenon-based machines with an overall number of 121 cores. To present an example, we changed in the reference protocol of UZH the age classification with a parameter $\delta_{age} \in [-4, 4]$, similarly also the classification with respect to the AMH levels and AFC, and, as a treatment parameter, the administered doses of the stimulation drug.

Figure 17 shows the outcome of an execition of the MBD-ITP service, where 14 Pareto-optimal treatments were returned. Obviously, the reference treatment from UZH (dark blue) balances quite well its performance over all KPIs.

Also the other candidate treatments show interesting properties. For example, one treatment at the same time minimises the overall amount of drug used (saving, on average, 34.7% of stimulation drug with respect to the reference treatment) and maximises the number of cases in which it succeeds (34.1%, vs. 28% of the reference treatment), at the cost of allowing the retrieval of (on average) fewer mature oocytes (4.617 vs. 5.571 of the reference treatment) and to approach FSC less frequently (38.5% on average vs. 48.5% for the reference

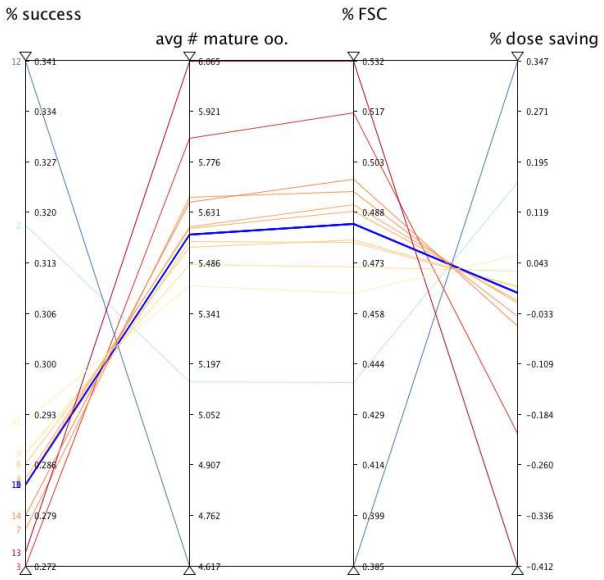


Figure 17: Pareto-optimal treatments computed by MBD-ITP. The reference treatment is in dark blue.

treatment).

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